

SUPPORT FOR THE AMENDMENTS

Claims 1 and 4 were previously canceled.

Claim 6 is presently canceled.

Claims 8, 9, 22, and 26 are amended.

Claims 30-33 are added.

Support for the amendment of Claims 8 and 9 is provided by the specification at, for example, paragraph [0026]. Support for the amendment of Claims 22 and 26 is provided by the specification at, for example, paragraph [0030]. New Claims 30-33 are supported by the specification at, for example, paragraph [0026] and the Examples (see Examples 1, 2, 4, and 5; see amendments filed July 15, 2008 and February 26, 2009, for the amendments to the specification) as summarized in the table below:

First Composition (A)		Example 1	Example 2	Example 4	Example 5
Sodium fluoride	wt%	2	2	0.21	0.05
	mol/L	0.48	0.48	0.51	0.01
phosphoric acid	wt%	1.6	3	0.5	0.2
	mol/L	0.16	0.30	0.05	0.02
Molar ratio of sodium fluoride to phosphoric acid		3.00	1.60	1.00	0.50

No new matter has been added by the present amendments.

REMARKS

Claims 2, 3, 5, and 7-33 are pending in the present application.

Applicants wish to thank Examiner Sutton and Examiner Lundgren for the helpful and courteous discussion with their undersigned Representative on September 8, 2010. During this discussion, various arguments (including those presented herein) were discussed. The content of this discussion is believed to be accurately reflected by the comments presented herein. Reconsideration of the outstanding rejections is requested in view of the amendments and remarks herein.

At the outset, Applicants note that the Examiner has modified the rejections of record to rely upon the primary combination of Usen et al and Tomlinson et al and has removed reliance upon Winston et al. Nonetheless, the Examiner apparently felt compelled to address the experimental evidence and our arguments based on the rejection over Winston et al in view of Usen et al and Tomlinson et al in the Office Action mailed May 17, 2010, and in so doing has clouded the record as it is unclear whether the rejections based on Winston et al are adhered to or are withdrawn. In view of the procedural uncertainty, Applicants provide the following remarks addressing Office Action as if there were two sets of rejections (1) based on the primary combination of Usen et al and Tomlinson et al and (2) based on Winston et al in view of Usen et al and Tomlinson et al.

The rejections of:

- (a) Claims 2, 3, 5-7, 9, 12, 13, and 26-29 under 35 U.S.C. §103(a) over (i) Usen et al (US 5,605,675) in view of Tomlinson et al (US 4,048,300) or (ii) Winston et al (US 5,858,333) in view of Usen et al (US 5,605,675) and Tomlinson et al (US 4,048,300);
- (b) Claims 14-17 and 21 under 35 U.S.C. §103(a) over (i) of Usen et al (US 5,605,675) in view of Tomlinson et al (US 4,048,300) and further in view of Grabenstetter et al (US 4,083,955) or (ii) Winston et al (US 5,858,333) in view of Usen et al (US 5,605,675) and Tomlinson et al (US 4,048,300) and further in view of Grabenstetter et al (US 4,083,955); and
- (c) Claims 8, 10, 11, 18-20, and 22-25 under 35 U.S.C. §103(a) over (i) Usen et al (US 5,605,675) in view of Tomlinson et al (US 4,048,300) and further in view of Wiesel (US 6,287,120) and Grabenstetter et al (US 4,083,955) or (ii) Winston et al (US 5,858,333) in view of Usen et al (US 5,605,675) and Tomlinson et al (US 4,048,300) and further in view of Wiesel (US 6,287,120) and Grabenstetter et al (US 4,083,955),

are respectfully traversed.

Regardless, of whether or not the outstanding rejections rely upon Winston et al, Applicants submit that the rejections are without merit and are rebutted by the evidence of record as supplemented by the revised Declaration under 37 C.F.R. §1.132 submitted herewith.. Specifically, the claimed invention is distinct from the cited art in that the art does not disclose alternately applying the separate compositions (Claims 8 and 9) or compositions meeting the requirements of (A) and (B) which are maintained discretely (Claim 8). Indeed,

Winston et al and Usen et al fail to disclose alternately applying the separate compositions as claimed and also fail to disclose the pH of the separate compositions and/or the molar ratios.

Tomlinson et al discloses alternate application of a composition, but merely describe monofluorophosphate as one of fluorides and is silent about calcium salts of polyol phosphate. Accordingly, the skilled artisan would not expect the claimed compositions Part A and B as claimed or alternately applying thereof to thereby maximum fluorine uptake. Further, Tomlinson fails to disclose the molar ratios as presently claimed.

In the outstanding Office Action, the Examiner improperly disregards these deficiencies and maintains that the alternate application of the claimed compositions Part A and B and the results flowing therefrom are obvious and/or expected. Applicants submit that this is not the case for the numerous reasons of record. Further, Applicants have already provided considerable evidence to illustrate the benefits obtained from the claimed invention as compared to the closest prior art examples. Indeed, in the Declaration accompanying the response filed January 25, 2010, in paragraphs 10-17, a comparison was provided of a single composition (i.e., mixed application), which reflects the disclosure of Usen et al, to the presently claimed alternate application. Illustrated in Table 4 is that the composition of the claimed invention provides a significant improvement in the fluorine uptake and HAP surface.

The Declaration accompanying the response filed January 25, 2010, also provides clear evidence of the importance of a second composition containing a monofluorophosphate and a calcium salt of polyol phosphate wherein an aqueous solution of said second composition has a pH value ranging from 6 to 12. Indeed, the criticality of this combination is provided by the data in Table 4, as well as the detailed experiments in paragraphs 14-17. In paragraph 17, it is clearly summarized that a mixed solution having a low pH is due to the

presence of calcium nitrate or calcium lactate would not be suitable for repairing teeth would not be repaired, but rather would melt teeth. Neither Usen et al nor Tomlinson et al specifically disclose or exemplify a second composition containing a monofluorophosphate and a calcium salt of polyol phosphate wherein an aqueous solution of said second composition has a pH value ranging from 6 to 12, much less disclose or suggest this result.

The Examiner makes a series of allegations in the 10-15 of the outstanding Office Action, many of which find no merit. Indeed, with respect to Table 1 in the Declaration accompanying the response filed Janaury 25, 2010, Applicants compared the claimed method with Winston et al. Winston et al. defines the pH of composition (i.e. pH=5.5). This is because hydroxyapatite (HAP) is decalcified (i.e. “melted”) when HAP is treated under the pH of 5.5 or below. Specifically, the solubility of hydroxyapatite is dramatically enhanced below pH of 5.5. Thus, Comparative Examples B1 and B2 were conducted under the pH condition in which the composition of Winston et al. actually works. Without this correction, there would be nothing to compare as the HAP would be melted.

The Examiner also alleges that Table 1 does not show unexpected results because the fluoride uptake of Comparative Example B2 is 10% higher than that of Comparative Example B1. Applicants respectfully question the relevance of this statement as the Examiner is comparing the two comparative examples rather than comparing the comparative examples to the example of the present application. When properly comparing the Example (fluorine uptake =  $2.00 \mu\text{g}/\text{cm}^2$ ) with Comparative Example B2 (fluorine uptake =  $0.82 \mu\text{g}/\text{cm}^2$ ) or with Comparative Example B1 (fluorine uptake 1 =  $0.75 \mu\text{g}/\text{cm}^2$ ), the fluorine uptake is almost 250% higher. As summarized in paragraphs 6-8 and further supported by paragraphs 9-10 of the Declaration accompanying the response filed Janaury 25, 2010, a fluorine uptake of 250% higher when using the alternate application as presently claimed is in

no way expected in view of the disclosure of, not just Winston et al, but also of Usen et al, Tomlinson, Grabenstetter, and Wiesel.

With respect to the 10% difference in the fluorine uptake in the treatment with a mixed solution in Comparative Example B2 and that in Comparative Example B1, Applicants submit that this is a result caused by the existence of MFP in Comparative Example B2. In premixed treatment, because MFP accelerates formation of crystal of calcium phosphate and calcium fluoride, fluorine intake is decreased. This is important and represents yet another distinction from the art as the compositions of Usen et al and Winston et al are premixed on pre-mixing, no one in the art would think to add MFP into the compositions in Usen et al and Winston et al and Comparative Example B2 illustrates the reason why.

The Examiner has alleged that Applicant should conduct experiments under the same pH condition as claimed method. Therefore, Applicants did conduct these additional comparative experiments and provide the results in Tables 3 and 4. The pH of Comparative Example C1 after mixing is 3.1. The pH of Comparative Example C2 after mixing is 4.00. When these mixtures were applied on HAP pellet, HAP surface was melted (see Table 4). This means composition in Winston et al. can not be the same pH of present invention. Thus, the allegations by the Examiner with respect to the pH find no merit.

The fundamental problem is that the Examiner believes that he has made a proper *prima facie* case of obviousness and that this ends the analysis. Applicant certainly disputes the fact that a *prima facie* case of obviousness exists and submit that determination of such a case would only be the first step in the analysis. Applicants remind the Examiner that “Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. “Evidence that a compound is unexpectedly superior in one of a spectrum of common

properties . . . can be enough to rebut a *prima facie* case of obviousness.” No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)” Thus, the experimental data presented in the Declaration accompanying the response filed January 25, 2010, and the Declaration **submitted herewith**, clearly illustrates that substantial benefits flowing from the claimed method, which are enough to rebut a *prima facie* case of obviousness.

To further illustrate the differences between the claimed invention, in the Declaration submitted herewith, Applicants provide new paragraphs 18-20 to further illustrate the unexpected results flowing from the claimed invention.

The Examiner cites and relies upon Tomlinson et al as disclosing alternative treatment with two compositions. However, Tomlinson et al merely describe monofluorophosphate as one of the fluorides and is silent about calcium salts of polyol phosphate. This deficiency is significant as a critical distinction giving rise to an unexpected result is in the specific alternately application of a first composition (A) and a second composition (B) to a tooth:

(A) a first composition containing an inorganic fluoride and an inorganic phosphoric acid or a salt thereof wherein an aqueous solution of said first composition has a pH value ranging from 2 to 6; and

(B) a second composition containing a monofluorophosphate and a calcium salt of polyol phosphate, wherein an organic acid constituting the calcium salt of organic acid has a pKa value ranging from 3 to 11, or at least one pKa value ranging from 3 to 11 when the organic acid has plural pKa values wherein an aqueous solution of said second composition has a pH value ranging from 6 to 12.

Indeed, in the Example 12 of Tomlinson et al calcium nitrate is used. When calcium nitrate was used for the substitution of calcium glycerophosphate, the surface of HAP was

melted. These results are shown in Table 3 and 4 of the Declaration submitted herewith (see Comparative Examples C1 and C2). Further, in paragraph 18 of the Declaration submitted herewith Applicants provide Figures 2-1 through 2-3, which illustrate the effects of the Comparative Example 1 in relation to the Example of the present application.

Specifically:

Fig. 2-1



Fig. 2-1 shows HAP powder before treatment. Columnar crystals of HAP are observed.



Fig. 2-2

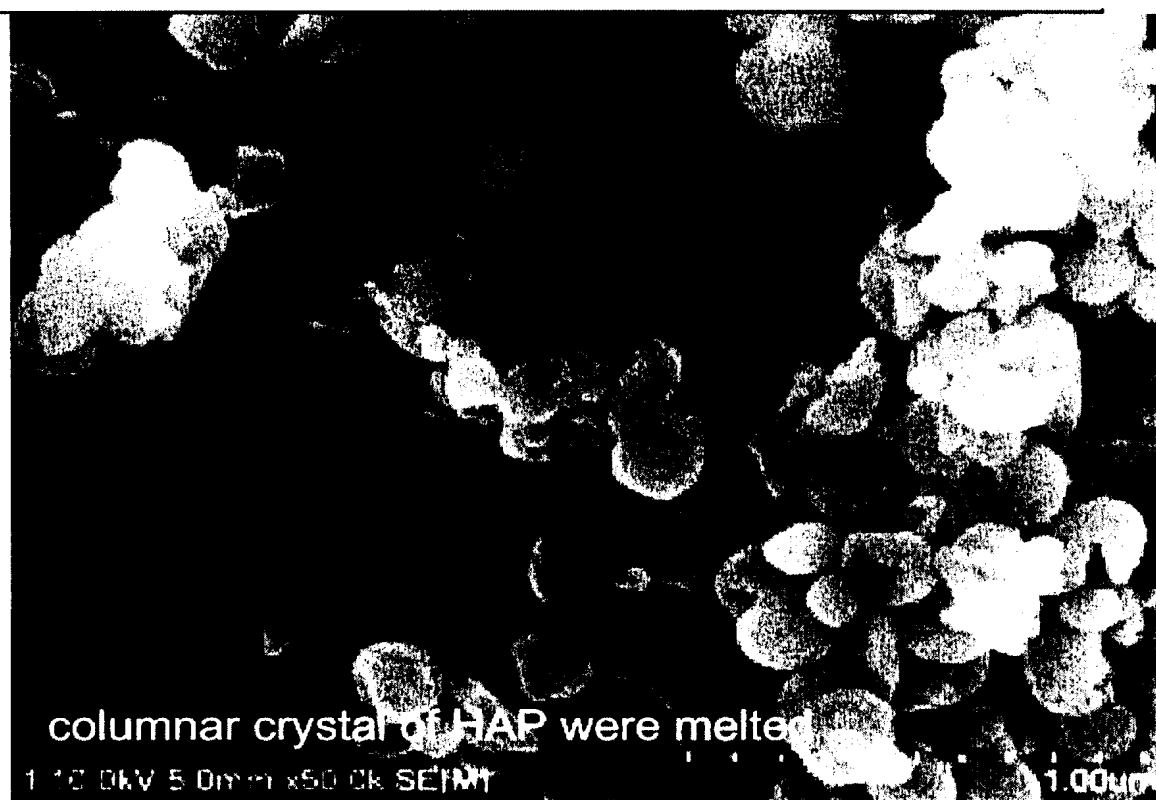


Fig. 2-2 shows HAP powder after treatment by the composition identified as Comparative Example C1 in Table 3 above. Columnar crystals of HAP are melted. This result shows that HAP is melted when Comparative Example C1 is applied by alternative treatment. In Table 4 above, fluoride uptake of Comparative Examples C1 and C2 are 8.25 and 6.21, respectively. These values look higher than the example of the claimed invention at first glance. However, this does not tell the complete story as HAP was melted and the calcium ion is released from HAP. The calcium ion is combined with fluoride and becomes calcium fluoride on the surface of HAP. Calcium fluoride is easily dissolved in saliva and, as a result, calcium fluoride in the saliva was detected for fluoride uptake.

Fig. 2-3

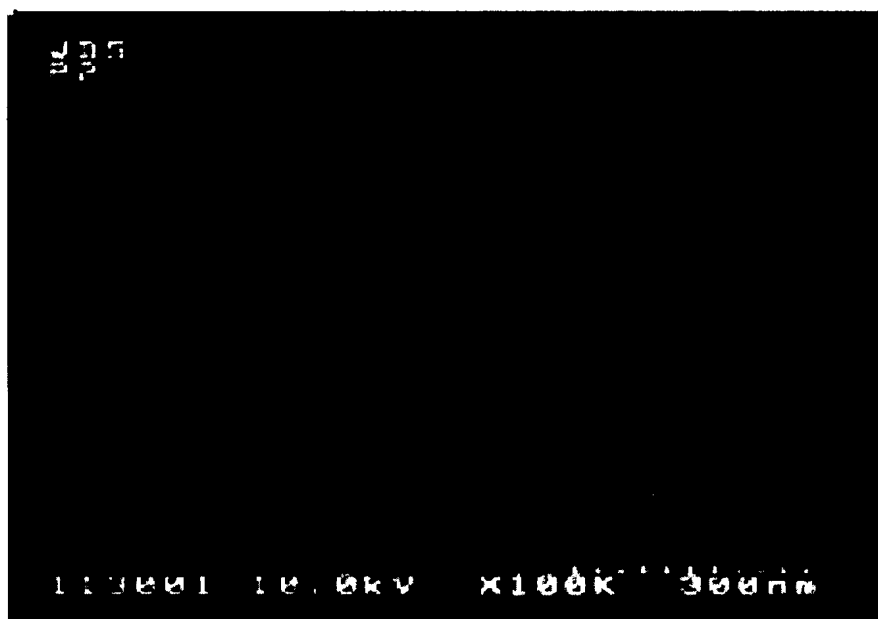


Fig. 2-3 shows HAP powder after treatment by the composition identified as Example in Table 3 above. It is observed that columnar crystal of HAP was not melted and many small crystals were attached on the surface of HAP. These small crystals contain “calcium fluoride”, “hydroxyapatite”, and “calcium phosphate”. When calcium fluoride coexists with hydroxyapatite and/or calcium phosphate, calcium fluoride is hardly dissolved into saliva and fluoride is taken into HAP. The fluoride taken into HAP forms into FHAP ( $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ ).

From the foregoing, it is shown that Comparative Examples C1 and C2, which contain calcium nitrate is substantially inferior to the Example if the presently claimed invention containing calcium glycerophosphate. As stated in paragraph 18 of the Declaration submitted herewith, when this evidence is taken together with the data in Table 4 the criticality in using calcium glycerophosphate is clearly demonstrated, which represents and unexpected result in view of the cited art.

Tables 6 and 7 (below) showing the solubility and concentration in saliva:

Table 6

	Solubility
Calcium fluoride	18 mg/l
Hydroxyapatite	1 to 3 mg/l
Calcium hydrogen phosphate	200 mg/l

Table 7

	concentration in saliva
Calcium	20 to 30 mg/l
Fluoride	0.03 mg/l
Phosphate	200 to 300 mg/l

Since the concentration of fluoride in saliva is low, calcium fluoride is easily dissolved into saliva. In contrast, because concentration of phosphate in saliva is high, calcium hydrogen phosphate is hardly dissolved into saliva. Therefore, calcium fluoride must coexist with hydroxyapatite and/or calcium phosphate for re-calcification (re-mineralization).

Figures 3-1 and 3-2 provide an illustration of the scheme to provide a better understanding.

Fig. 3-1 Comp. Ex. (calcium nitrate)

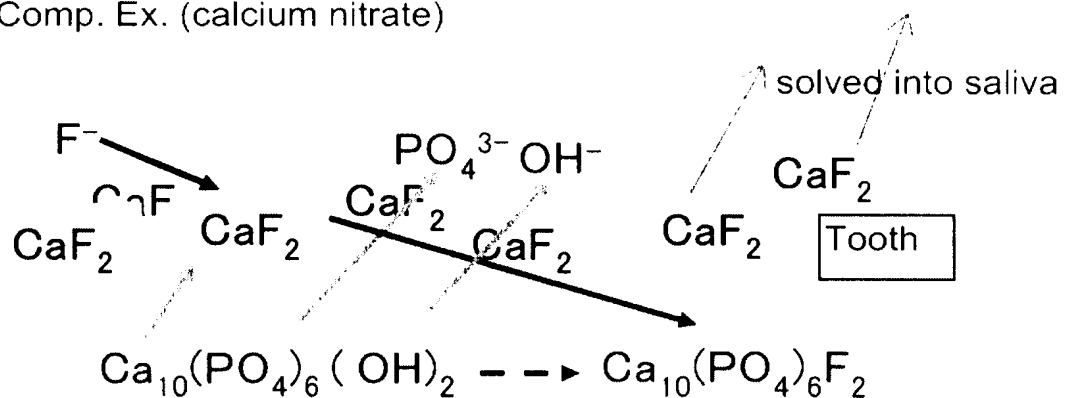
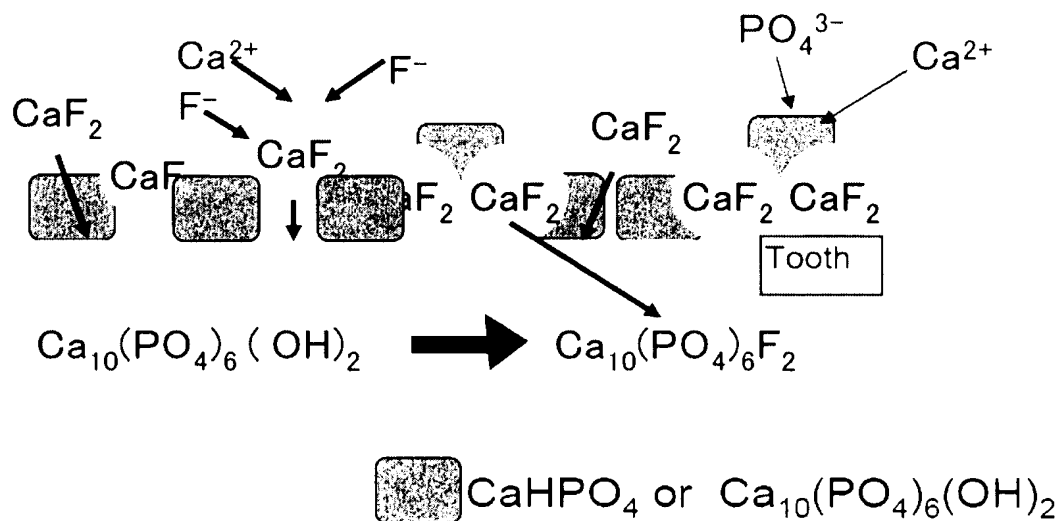


Fig. 3-2 Examples. (calcium glycerophosphate)



Thus, it is summarized in paragraph 20 of the Declaration submitted herewith that the alternative treatment with two compositions as claimed, an unexpected result was obtained when the composition contains a calcium polyol phosphate (such as calcium glycerophosphate). Since US 4,048,300 (Tomlinson) does not disclose calcium polyol phosphate and US 5,858,333 (Winston) as well as US 5,605,675 (Usen et al) do not disclose alternative treatment, claimed method is not obvious. Moreover, the claimed invention provides an unexpected result when considering the additional disclosures of US 4,083,955 (Grabenstetter) and US 6,287,120 (Wiesel).

Thus, the foregoing, new data when taken with the evidence provided in paragraphs 5-17 of the Declaration submitted herewith clearly rebut even a *prima facie* case of obviousness.

To ensure completeness of the record, Applicants again provide the following additional remarks in response to the rejections of record in view of paragraphs 5-17 of the Declaration submitted herewith, with reference to their prior iterations.

Specifically, the first Yamagishi Declaration reveals the fluoride uptake of the composition containing monofluorophosphate in Winston et al's composition in the Comparative Example B2 as well as Winston et al's composition, i.e., the Comparative Example B1. Applicants submit that Comparative Example B2 shows the comparison to the composition as stated in the Advisory Action.

Indeed, the labels as “part A” and “Part B” described in the first Yamagishi Declaration adopt those in Winston et al (US 5,858,333 and WO1998/13012), which direct to a second composition (B) and a first composition (A) in the present invention, respectively. In fact, the present invention reverses the wording “A” and “B” with respect to Winston et al. Rather than focusing on the label applied to the individual compositions, it is necessary to actually look at the components in the individual compositions.

In the composition of the Comparative Example B1, B2 and B3, Part A contains calcium component. Moreover, the Part A of the Comparative Example B2 includes monofluorophosphate and thus it is believed to represent a comparison with Winston et al. It is further noted that Winston et al do not disclose any example in which Part A contains both monofluorophosphate and calcium component.

Winston et al describe two composition A and B are mixed and then applied. Therefore, monofluorophosphate is added to Part A containing calcium component in Winston et al to thereby immediately precipitate calcium phosphate. It is clear from Comparative Example B2 that adding monofluorophosphate to calcium-containing Part A, i.e., mixing Part A and B in Winston et al, is not effective for fluorine uptake.

Both Winston et al and Usen et al disclose the Part A and B are mixed and then applied and therefore monofluoro -phosphate is added to the Part A containing calcium to thereby decrease an uptake amount of fluorine. The skilled artisan would not expect to attain

excellent fluorine uptake by alternately applying the separate Part A and B in which Part A contains monofluorophosphate based on Winston et al. Winston et al is silent about claimed composition of Part A and Part B and alternately applying of them.

Tomlinson et al discloses the alternately apply of the composition, but merely describe monofluorophosphate as one of fluorides and is silent about calcium salts of polyol phosphate. Accordingly, the skilled artisan would not expect the claimed compositions Part A and B or alternately applying thereof to thereby maximum fluorine uptake. None of the cited references disclose when monofluorophosphate is contained in the composition, fluorine uptake can be attain only by alternately applying of the composition Part A and B.

To further illustrate the non-obviousness of the presently claimed invention, Applicants submitted a second Yamagishi Declaration.

In the second Yamagishi Declaration, the experiment provided in the first Yamagishi Declaration has been updated to include the pH of the individual compositions (i.e., part A and part B; see Table 1). In addition, the Yamagishi Declaration provides two new experiments (see paragraphs 11-16).

As previously established in the response filed on July 15, 2008 and February 26, 2009, Winston et al fail to disclose or suggest alternately applying a first composition (A) and a second composition (B) to a tooth where the first composition (A) contains a fluoride ion-supplying compound and an inorganic phosphoric acid or a salt thereof; and the second composition (B) contains a calcium salt of organic acid, wherein an organic acid constituting the calcium salt of organic acid has a pKa value ranging from 3 to 11, or at least one pKa value ranging from 3 to 11 when the organic acid has plural pKa values.

Winston et al disclose one-part or two-part products for remineralizing or mineralizing teeth (see Abstract). However, throughout the specification, Winston et al

disclose that “when the product... is ready to be used, the cationic and anionic components are mixed together with water and/or saliva to form the mixed aqueous composition... The anionic and cationic components are mixed only when the components are introduced into the oral cavity or immediately before their introduction into the oral cavity” (see page 23, line 29 to page 24, line 6). Further, at page 36, lines 11-29, Winston et al specifically disclose “When using the two-part aqueous products of this invention, the time period between the mixing of the first and second parts and the application of the resulting mixed aqueous composition to the teeth should not exceed 1 minute.... An important feature of the present invention lies in the mixing of the anionic and cationic components and the quick and timely application of the resulting mixed composition to the tooth...”

In view of the foregoing and the remainder of the disclosure by Winston et al, including the Examples, it is clear that the two-part system disclosed therein is either mixed simultaneously (at best in the oral cavity as opposed to on the tooth surface) or pre-mixed before application to the oral cavity or teeth. In contrast, the claimed invention requires the alternate application of composition (A) and composition (B). The meaning of “alternate application” is clear from the disclosure of the present application and means that either composition (A) or composition (B) is applied to the teeth followed after a certain time interval the application of the other composition (see, for example, paragraphs [0011], [0019], and [0032]-[0034], and the Examples). Winston et al does not disclose or suggest the alternate application as claimed.

The foregoing distinction is important for two reasons. First, the fact that Winston et al does not disclose or suggest the alternate application as claimed means that this reference cannot anticipate the claimed invention. Second, Applicants submit that the claimed method provides a substantial unexpected advantage with respect to fluorine uptake as compared to

either simultaneously applying (A) and (B) or pre-mixing (A) and (B) prior to application, each of which is more representative of the disclosure of Winston et al.

In the Office Action mailed October 31, 2008, the Examiner acknowledged that Winston et al fails to disclose the method of alternately applying the separate compositions. In an attempt to compensate for this deficiency, the Examiner cites Tomlinson et al, which Applicants submit does not.

Winston et al disclose a two-part product containing a cationic part and an anionic part. The anionic part may contain at least one water-soluble fluoride salt. These salts are preferably present in the anionic part rather than in the cationic part so as to avoid formation of sparingly soluble calcium fluoride (see, column 8, lines 53-59). Although the cationic part may contain MFP (monofluorophosphate) with calcium salt, Winston et al specifically disclose that inclusion of MFP in the cationic part is less desirable due to the potential loss of fluoride (see, column 9, lines 17-21).

Therefore, Winston et al discloses the product which includes a cationic part containing calcium supplier and an anionic part containing sodium fluoride and MFP, while the reference does not specifically disclose a product including fluoride in both parts or a product including both MFP and calcium salt in one part, but rather discloses that such a product would not be desirable and/or would be expected to have poor fluorine uptake properties.

Example 12 of Tomlinson et al do not include a calcium salt of polyol phosphate or organic acid. The product of Tomlinson et al also do not contain fluoride in both parts. Additionally; in the second solution of Example 12 of Tomlinson et al, calcium phosphate should be immediately precipitated and only a very small amount of calcium remains in supernatant. The specification of Tomlinson et al does not provide any further clarity with



respect to the specific ingredients of the compositions making up the claimed product. And thus, fails to compensate for the deficiencies in Winston et al.

In contrast to Winston et al, the claimed two-part product includes composition (A) containing an inorganic fluoride and composition (B) containing MFP and calcium salt of polyol phosphate, which thus includes fluoride in both parts and contains both MFP and calcium salt in one part. To demonstrate the unexpected results flowing from the claimed invention as compared to the stated expectation in Winston et al, Applicants again point to the first Yamagishi Declaration and the explanation of the probative value of this declaration provided above. Applicants further direct the Examiner's attention to the second Yamagishi Declaration, in which the declarant again reports on a comparison of the claimed product to Example 5 of Winston, which, of the Examples, provides the highest increase in hardness (see Table VII).

As shown in Table 1 of the second Yamagishi Declaration, the amount of fluorine uptake derived from the claimed product was nearly three times larger ( $2.00 \mu\text{g}/\text{cm}^2$  vs.  $0.75 \mu\text{g}/\text{cm}^2$ ) than that derived from Comparative Example B1 (Example 5 composition of US 5,858,333 ("Winston")). Comparing with the Comparative Example B2, which is the Example 5 composition of Winston further containing MFP in Part A, the claimed product resulted in more than two-fold fluorine uptake ( $2.00 \mu\text{g}/\text{cm}^2$  vs.  $0.82 \mu\text{g}/\text{cm}^2$ ). In Comparative Example B3, in which MFP was contained in Part A as the only fluorine supplier, fluorine uptake was poor (0.05). (see paragraph 7 of the second Yamagishi Declaration)

On the basis of these data, the declarant of the Yamagishi Declaration states:

Winston disclose that the cationic part (i.e., Part A) may contain MFP (monofluorophosphate) with calcium salt, but it is less desirable due to the potential loss of fluoride (see, column 9, lines 17-21). As a result, Winston does not provide any Examples in which MFP is used. Thus,

based on the disclosure of Winston, the artisan would have expected that the presence of MFP in the cationic part (i.e., Part A) would result in the loss of fluoride and would be dissuaded from using MFP in this part. Indeed, as illustrated in Comparative Example B2 above, adding MFP to part A of Example 5 of Winston resulted in poor fluorine uptake.

In contrast to the expectation presented by the disclosure of Winston, the claimed product, which includes MFP with calcium salt (i.e., in Part A), leads to excellent fluoride uptake rather than resulting in loss of fluoride (see, Table 1 above). Such excellent fluoride uptake (i.e., two-fold over Winston's composition with MFP in Part A and nearly three-fold of Winston's exemplified composition) provided by the claimed invention is in no way expected from the disclosure of Winston.

This result is also unexpected even when considering the disclosures of US 4,048,300 (Tomlinson), US 4,083,955 (Grabenstetter), and/or US 6,287,120 (Wiesel). This conclusion remains true even when considering newly cited US 5,605,675 (Usen et al). (see paragraph 9 of the second Yamagishi Declaration)

The Examiner is reminded that “[a] prima facie case of obviousness ... is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties.” See MPEP §2144.09 (citing *In re Paesch*, 315 F.2d 381 (C.C.P.A. 1963)). Applicants submit that the results summarized above and provided in the second Yamagishi Declaration establish that the claimed dental product possesses unexpected advantages and superior properties as compared to the products disclosed in Winston et al, even when viewed with Tomlinson et al, Usen et al, Grabenstetter et al and Wiesel.

The Examiner is further reminded of the fact that Winston et al fail to disclose the alternate application of the two compositions of the presently claimed invention. The advantages of the same were demonstrated in the Declaration under 37 C.F.R. §1.132 submitted on July 15, 2008 (“the July 15, 2008 Declaration”). In the July 15, 2008 Declaration, Applicants showed the following comparison of the results obtained as a measure of fluorine uptake ( $\mu\text{g}/\text{cm}^2$ ) for the claimed method and two methods that are representative of the disclosure of Winston et al:

	Alternately applying (A) and (B) <sup>i</sup>		Simultaneously applying (A) and (B) <sup>ii</sup>		Pre-mixing (A) and (B) <sup>iii</sup>	
	1 min.	3 min.	1 min.	3 min.	1 min.	3 min.
Example 1	5.2	13.5	0.3	0.4	0.1	0.2
Example 2	5.8	15.8	0.6	0.6	0.2	0.2
Example 3	4.9	11.5	0.8	0.9	0.3	0.4
Example 4	0.6	5.2	0.2	0.2	0.1	0.1
Example 5	0.3	3.8	0.1	0.1	0.1	0.1

i) Alternately applying (A) and (B): alternately at 10 second intervals

ii) Simultaneously applying (A) and (B): mixed at teeth

iii) Pre-mixing (A) and (B): pre-mixed for 10 seconds prior to application to teeth

These results clearly evidence the unexpected superiority of the claimed method with respect to fluorine uptake is demonstrated as compared to method representing the disclosure of Winston et al, even when viewed with Tomlinson et al, which further rebuts the alleged obviousness rejection.

Applicants now take the demonstration of unexpected results one step further. In the second Yamagishi Declaration, the Declarant provides two additional experiments.

In the first experiment appearing in paragraphs 11-13 of the second Yamagishi Declaration, a comparative experiment suggested by the Examiner in the Interview Summary dated November 5, 2009, was performed. Specifically, each pH of Composition A and B was adjusted to be same as those of examples in the claimed invention. The pH values of each mixed solution were shown in Table 3 since pH values would have an effect on a production of a salt of calcium phosphate.

The experimental result in Table 4 show that fluorine uptake amount of Comparative Examples C1 and C2 could be increased since each pH thereof was very low. However, it

was also clearly shown that HAP pellets were apparently melted because of their low pH. Thus, the effect of monofluorophosphate could not be compared since a salt of calcium phosphate was not produced. (see paragraph 13 of the second Yamagishi Declaration)

Since the HAP pellets were melted in the experiment appearing in paragraphs 11-13 of the second Yamagishi Declaration, the declarant investigated the buffering capacity of the mixed solution of Compositions A and B (see paragraphs 14-16 of the second Yamagishi Declaration). In these experiments a solution containing calcium nitrate, calcium lactate or calcium glycerophosphate was added to an acidic solution of sodium fluoride containing phosphate (pH 3.7) and each pH was measured. The results for these experiments are illustrated in Table 5 and Figure 1 of the second Yamagishi Declaration.

In paragraph 17 of the second Yamagishi Declaration, the declarant sets forth the relevance of the newly added experimental data stating:

In accordance with the foregoing experimental results, the mixed solution has low pH in Comparative Examples C1 and C2 because its buffering capacity of calcium salts included therein and therefore teeth would not be repaired, but melted. In addition, Comparative Examples C1 and C2 do not show the effect of the claimed invention, which effects are to increase production of a salt of calcium phosphate and to increase fluorine uptake.

This result is also unexpected even when considering the disclosures of US 4,048,300 (Tomlinson), US 4,083,955 (Grabenstetter), and/or US 6,287,120 (Wiesel). This conclusion remains true even when considering newly cited US 5,605,675 (Usen et al).

Moreover, Applicants submit that in the presently claimed invention, the product of the present invention has the composition A having pH of 2 to 6 and composition B having pH of 6 to 12 and alternately applied to teeth, to thereby promptly form a calcium phosphate on teeth and enables uptake of fluorine.

On the other hand, Winston et al uses calcium nitrate and calcium lactate and these calcium salts have a an acid with pKa of less than 3, about 1, and they have no buffering capacity. Accordingly, when the compositions A and B of the Winston et al are set to pH of the present invention and alternately applied onto teeth, nitric acid or lactic acid would be produced and then teeth would be melted. In cased where the compositions A and B of Winston et al is set to pH of the present invention and are mixed before applying teeth, calcium phosphate would not be produced and teeth would be damaged.

The compositions of the present invention are formulated so that calcium phosphate and calcium phosphate is promptly formed and uptake of fluorine is increased. Therefore, when the compositions of the present invention are employed in Winston et al's method, calcium phosphate and calcium fluoride are promptly agglutinated as soon as mixed and therefore it is difficult to form calcium phosphate and calcium fluoride on teeth. Winston et al's composition is formulated in order to slowly form calcium phosphate and calcium fluoride and to form calcium phosphate and calcium fluoride as soon as applied on teeth. It differs between Winston et al and the present invention in applied method and also in control of formation of calcium phosphate and calcium fluoride. Accordingly, Winston et al or Usen et al does not teach a method for prompt formation of calcium phosphate and calcium fluoride.

Tomlinson et al specifically discloses alternate apply of the compositions A and B in example 12. While the first composition was prepared to include phosphoric acid and sodium fluoride and have pH of 3, the second composition was prepared includes calcium nitrate and sodium hydric orthophosphate and have pH of 5. After standing, the supernatant was separated and its pH was adjusted to 7. Then, the first and second compositions are alternately applied to thereby form fluoroapatite.

However, Tomlinson et al differs from the present invention on the points that pH of the second composition is adjusted to 5 in order to form a solid of calcium hydric phosphate and then adjusted to 7 in order to stabilize a solid of calcium hydric phosphate. On the other hand, in the present invention, pH of the second composition is first adjusted to 6 to 12, none of calcium hydric phosphate is formed and then alternately applied to teeth, to thereby enable prompt formation of calcium phosphate on teeth and up take of fluorine. Moreover, Tomlinson et al's composition is prepared in two steps and needs time to form calcium hydric phosphate in the second composition, while the composition B of the present invention is prepared in one step and does not need such a time.

Accordingly, the presently claimed invention and the advantages flowing therefrom are clearly not disclosed or suggested by Winston et al, even when viewed with Tomlinson et al and Usen et al. The Examiner is again reminded that "[a] prima facie case of obviousness ... is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties." See MPEP §2144.09 (citing *In re Paesch*, 315 F.2d 381 (C.C.P.A. 1963)). Applicants submit that the results summarized above and provided in the second Yamagishi Declaration establish that the claimed dental product possesses unexpected advantages and superior properties as compared to the products disclosed in Winston et al, even when viewed with Tomlinson et al and Usen et al.

Usen et al suffers from the same deficiency as Winston et al, i.e., failure to disclose alternate treatment. As such, all the arguments above are equally applicable to Usen et al as the primary reference as they were with Winston et al.

Further, with respect to the claimed molar ratio of the inorganic fluoride to inorganic phosphoric acid or a salt thereof ranging 0.1 to 10 in the first composition (A) recited in amended claims 8 and 9, this limitation is not disclosed or suggested by Tomlinson et al and

Usen et al. This represents yet another reason why the claimed invention is not obvious over the cited art.

Specifically, the alternative application of the first composition (A) and the second composition (B) of the present invention forms calcium phosphate on teeth. Melting of the formed calcium phosphate and teeth, i.e., hydroxyapatite, can be prevented by the buffering ability of polyolphosphate. When the molar ratio of an inorganic fluoride to an inorganic phosphoric acid is increased, the amount of inorganic fluoride is increased and formation of calcium fluoride is promoted, but the amount of the formed calcium phosphate is reduced due to the decrease of inorganic phosphoric acid.

In Example 1, the content of sodium fluoride is greater than phosphoric acid and therefore the amount of the fluorine uptake is increased and calcium fluoride is formed in a high amount. As compared with Example 1, the molar ratio of an inorganic fluoride to an inorganic phosphate is smaller in Examples 3 and as a result, fluorine uptake is slightly reduced.

On the other hand, in Example 5, the molar ratio of an inorganic fluoride to an inorganic phosphoric acid is 0.5. Such a small molar ratio causes reduced fluorine uptake, but sufficiently forms calcium phosphate, to thereby improve the symptom of dentin hyperesthesia. Calcium fluoride improves the acid resistance of hydroxyapatite of teeth and calcium phosphate formed on teeth. However, calcium fluoride is easily dissolved in oral cavity due to low content of calcium fluoride in saliva.

For sake of reference, Applicants provide the following summary table, which is based on Examples 1, 2, 4, and 5 in the specification:

<b>A</b>		Example 1	Example 2	Example 4	Example 5
Sodium fluoride	wt. %	2	2	0.21	0.05
	mol/L	0.48	0.48	0.05	0.01
Phosphoric acid	wt. %	1.6	3	0.5	0.2
	mol/L	0.16	0.30	0.05	0.02
<b>B</b>					
Calcium glycerophosphate	wt. %	3	50	1	1
	mol/L	0.14	2.38	0.05	0.05
MFP	wt. %	1	1	0.14	0.14
	mol/L	0.07	0.07	0.01	0.01

Fluoride uptake ( $\mu\text{g}/\text{cm}^2$ )	5.2	4.9	0.6	0.3
Subject symptom disappearance (persons) from table 1 in the specification	10	12	12	14
Molar ratio of inorganic fluoride to inorganic phosphoric acid or salt thereof	<b>3.00</b>	<b>1.60</b>	<b>1.00</b>	<b>0.50</b>

Thus, when the molar ratio of an inorganic fluoride to an inorganic phosphoric acid is more than 10, calcium fluoride is dissolved in saliva even though a great amount of calcium fluoride is formed. Moreover, when this molar ratio exceeds 10, an effect of improving symptom of dentin hyperesthesia is reduced. On the other hand, when the molar ratio of inorganic fluoride to inorganic phosphoric acid is less than 0.1, calcium phosphate is formed, but the amount of the calcium fluoride is smaller thereby reducing acid resistance.

The molar ratio of inorganic fluoride to inorganic phosphoric acid or a salt thereof preferably ranges from 0.1 to 10 in view of the point that the both calcium fluoride and calcium phosphate are formed and maintained. This effect is not disclosed or suggested by the cited art.

Grabenstetter et al and Wiesel fail to compensate for the deficiencies above in the combined disclosures of Winston et al and Tomlinson et al. Specifically, Grabenstetter et al



also does not disclose the product containing fluoride in both parts. Wiesel is only cited for referring to carrier, but offers nothing with respect to the aforementioned deficiencies.

In view of the foregoing, Applicants respectfully request that these grounds of rejection be withdrawn.

Applicants submit that the present application is now in condition for allowance.  
Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,  
MAIER & NEUSTADT, L.L.P.  
Stephen G. Baxter, Ph.D.



Vincent K. Shier, Ph.D.  
Registration No. 50,552

Customer Number

**22850**

Tel: (703) 413-3000  
Fax: (703) 413-2220  
(OSMMN 08/03)